

Marked-Up Version of the Claims

LISTING OF THE CLAIMS:

1. (currently amended) An antagonist of glucose-dependent insulintropic polypeptide (GIP) receptor consisting essentially of [a 24 amino acid polypeptide corresponding to positions 7-30 of the sequence of human GIP,] an amino acid sequence at least 95% identical to SEQ ID NO:2 or [rat GIP,] SEQ ID NO:8.

2-7 (canceled without prejudice and without disclaimer)

8. (currently amended) [An] A polypeptide antagonist of glucose-dependent insulintropic polypeptide (GIP) receptor effective to reduce glucose uptake from a mammalian intestine.

9. (currently amended) [An] A polypeptide GIP receptor antagonist according to claim 8, wherein said antagonist comprises [at least an effective number of amino acids] an amino acid sequence at least 95% identical to residues 7-30 [corresponding to those amino acids in posts 7-30] of SEQ ID NO:11 or SEQ ID NO:12 [GIP, SEQ ID NO:2 or effective alternative sequences thereto.]

10. (currently amended) [An] A polypeptide GIP receptor antagonist according to claim 8 wherein said antagonist comprises [a 24 amino acid polypeptide] an amino acid sequence identified as SEQ ID NO:2 [corresponding to positions 7-30 of the sequence of human GIP, SEQ ID NO:2 or effective alternative sequences thereto].

11. (currently amended) A pharmaceutical composition for [preventing, inhibiting or reducing obesity] improving glucose tolerance in an animal comprising:

an effective amount of an antagonist of glucose-dependent insulintropic polypeptide (GIP) that reduces or blocks [to inhibit, block or reduce] glucose absorption from the intestine of the animal, and

an acceptable pharmaceutical carrier.

12. (currently amended) A pharmaceutical composition according to claim 11, wherein the antagonist comprises [at least an effective number of amino acids corresponding to those] an amino acid sequence at least 95% identical to [amino acids in positions 7-30 of the sequence of human GIP,] SEQ ID NO:2 [or effective alternatives thereto].
13. (currently amended) A pharmaceutical composition according to claim 11, wherein the antagonist comprises an amino acid sequence at least 95% identical to [positions 24 amino acid polypeptide corresponding to positions 7-30 of the sequence of GIP or effective alternatives thereto] SEQ ID NO:8.
14. (original) A pharmaceutical composition according to claim 11, said pharmaceutical composition further including an inert pharmaceutical excipient selected from the group consisting of sweetening, flavoring, coloring, dispersing, disintegrating, binding, granulating, suspending, wetting, preservative and demulcent agents.
15. (original) An antagonist according to claim 8, wherein the antagonist is lyophilized.
16. (currently amended) An antagonist of claim 8 [15], wherein the [lyophilized] antagonist is prepared from a previously lyophilized preparation and reconstituted with a suitable diluent selected from the group consisting of normal saline, sterile water, glacial acetic acid, sodium acetate and combinations thereof.
17. (canceled without prejudice and without disclaimer)
18. (currently amended) An antagonist according to claim 8, wherein said antagonist comprises an amino acid sequence at least 95% identical to SEQ ID NO:8 [corresponding to positions 7-30 of the sequence of human GIP, SEQ ID NO:2 or effective alternative sequences thereto].

19. (currently amended) An antagonist according to claim 8, wherein said polypeptide antagonist comprises [a 24 amino acid polypeptide corresponding to positions 7-30 of the sequence of rat GIP,] SEQ ID NO:8[, or effective alternative sequences thereto].

20. (currently amended) [An antagonist] A pharmaceutical composition according to claim 11, wherein the antagonist is a polypeptide comprising an amino acid sequence at least 95% identical to [comprises at least an effective number of amino acids corresponding to those amino acids in positions 7-30 of the sequence of rat GIP,] SEQ ID NO:8 [or effective alternative sequences thereto].

21. (currently amended) [An antagonist] A pharmaceutical composition according to claim 11, wherein the antagonist comprises [a 24 amino acid polypeptide corresponding to positions 7-30 of the sequence of rat GIP,] an amino acid sequence identical to SEQ ID NO:8 [or effective alternative sequences thereto].

22. (currently amended) [A] An isolated polypeptide [having] comprising an amino acid sequence which specifically interferes with the biological activity of GIP when said polypeptide is administered [in an effective amount to an animal] to an animal in an amount effective to reduce intestinal uptake of glucose.

23. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid identical to [positions 7-30 of the sequence of human GIP,] SEQ ID NO:2 [or effective alternative sequences thereto].

24. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [24 amino acids corresponding to positions 7-30 of the sequence of human GIP,] SEQ ID NO:2[, or effective alternative sequences thereto].

25. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid sequence at least 95% identical to [positions 7-30 of the sequence of rat GIP,] SEQ ID NO:8[, or effective alternative sequences thereto].
26. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence identical to [24 amino acids corresponding to positions 7-30 of the sequence of rat GIP,] SEQ ID NO:8[, or effective alternative sequences thereto].
27. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid sequence at least 95% identical to [positions 16-30 of the sequence of human GIP,] SEQ ID NO:3[, or effective alternative sequences thereto].
28. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [15 amino acids corresponding to positions 16-30 of the sequence of human GIP,] SEQ ID NO:3[, or effective alternative sequences thereto].
29. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid sequence identical to [positions 16-30 of the sequence of rat GIP,] SEQ ID NO:9[, or effective alternative sequences thereto].
30. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [15 amino acids corresponding to positions 16-30 of the sequence of rat GIP,] SEQ ID NO:9[, or effective alternative sequences thereto].

31. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid sequence identical to [positions 10-30 [of the sequence] of human GIP,] SEQ ID NO:5[, or effective alternative sequences thereto].
32. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [21 amino acids corresponding to positions 10-30 of the sequence of human GIP,] SEQ ID NO:5[, or effective alternative sequences thereto].
33. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] an amino acid sequence identical to [positions 10-30 of the sequence of rat GIP,] SEQ. ID NO 10[:], or effective alternative sequences thereto].
34. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises [21 amino acids corresponding to positions] an amino acid sequence at least 95% identical to [21-30 of the sequence of rat GIP,] SEQ ID NO:10[, or effective alternative sequences thereto].
35. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises an amino acid sequence identical to [at least an effective number of amino acids corresponding to those amino acids in positions 21-30 of the sequence of rat GIP,] SEQ ID NO:13[, or effective alternative sequences thereto].
36. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [10 amino acids corresponding to positions 21-30 of the sequence of rat GIP,] SEQ ID NO:13[, or effective alternative sequences thereto].

37. (currently amended) A polypeptide according to claim 22, wherein said polypeptide comprises [at least an effective number of amino acids corresponding to those amino acids in] amino acid sequence of [positions 31-44 of the sequence of rat GIP,] SEQ ID NO:13[, or effective alternative sequences thereto].
38. (currently amended) A polypeptide according to claim 22, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [14 amino acids corresponding to positions 31-44 of the sequence of rat GIP,] SEQ ID NO:13[, or effective alternative sequences thereto].
39. (currently amended) A polypeptide having an amino acid sequence which specifically interferes with the biological activity of glucose-dependent insulintropic polypeptide (GIP) when said polypeptide is administered [in an effective amount to an animal] to a mammal in an amount effective to reduce absorption of glucose from the mammalian gut, said polypeptide comprising the amino acid sequence of [at least those amino acids corresponding to positions 7-9 of GIP,] SEQ ID NO 6.
40. (currently amended) A polypeptide according to claim 39, wherein the polypeptide comprises an amino acid sequence at least 95% identical to [24 amino acids corresponding to positions 7-30 of the sequence of human GIP,] SEQ ID NO:2[, or effective alternative sequences thereto].
41. (canceled without prejudice and without disclaimer)
42. (withdrawn without prejudice and without disclaimer) A polypeptide having an amino acid sequence having the ability to signal through a GIP receptor, said polypeptide comprising at least those amino acids corresponding to positions 7-15 of GIP, SEQ ID NO:4.
43. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to SEQ ID NO: 1, SEQ ID NO:

2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, and SEQ ID NO: 14, wherein said antagonist reduces intestinal uptake of glucose in a mammal when administered to said mammal.

44. (new) A pharmaceutical composition comprising a suitable pharmaceutical excipient and a polypeptide antagonist of glucose-dependent insulintropic polypeptide (GIP) receptor.

45. (new) An isolated polypeptide comprised within a pharmaceutical composition for administration to a mammal wherein said polypeptide antagonizes or interferes with glucose-dependent insulintropic polypeptide (GIP) binding to a GIP receptor in the mammal intestine to decrease glucose absorption from the intestine of the mammal.

46. (new) An isolated polypeptide comprised within a pharmaceutical composition for administration to a mammal exhibiting symptoms of type II diabetes wherein said polypeptide antagonizes or interferes with glucose-dependent insulintropic polypeptide (GIP) binding to a GIP receptor in the mammal intestine to decrease gut glucose uptake and normalize glucose tolerance in said mammal.

47. (new) An isolated polypeptide comprised within a pharmaceutical composition for administration to a mammal wherein said polypeptide antagonizes or interferes with glucose-dependent insulintropic polypeptide (GIP) binding to a GIP receptor in the mammal intestine to decrease serum glucose and serum insulin levels in a mammal, as compared to those serum glucose and insulin levels normally achieved in the mammal when untreated with said pharmaceutical composition.

48. (new) An isolated polypeptide comprised within a pharmaceutical composition for administration to a mammal wherein said polypeptide specifically antagonizes or interferes with glucose-dependent insulintropic polypeptide (GIP) binding to a GIP receptor in the mammal intestine to decrease serum insulin levels.

49. (new) An isolated polypeptide antagonist of glucose-dependent insulintropic polypeptide (GIP) receptor effective to reduce glucose uptake from a mammalian intestine and reduce serum insulin levels.

50. (new) A pharmaceutical composition for improving glucose tolerance in an animal comprising an effective amount of an antagonist of glucose-dependent insulintropic polypeptide (GIP) inhibitor that reduces or blocks glucose absorption from the intestine of the animal, and decreases serum insulin levels in the animal, in combination with an acceptable pharmaceutical carrier.

51. (new) An isolated polypeptide comprising an amino acid sequence which specifically interferes with the biological activity of GIP when said polypeptide is administered to an animal in an amount effective to reduce intestinal uptake of glucose and decrease serum insulin levels in the animal.

52. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to an amino acid residue selected from positions 1-30, 16-30, 10-30, 21-30, 31-44 and 7-9 of SEQ ID NO:11 or from SEQ ID NO:12, wherein binding of said antagonist to the GIP receptor inhibits insulin release without significantly affecting endogenous serum glucose concentration.

53. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to a group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 13, and SEQ ID NO: 14, wherein binding of said antagonist to the GIP receptor reduces intestinal uptake of glucose in a mammal when administered to said mammal.

54. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to a contiguous amino acid residue selected from positions 1-30, 16-30, 10-30, 21-30, 31-44 and 7-9 of SEQ ID NO:11 or SEQ ID NO:12, wherein binding of said antagonist to GIP receptor reduces intestinal uptake of glucose in a mammal when administered to said mammal.

55. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to a contiguous amino acid residue selected from positions 1-30, 16-30, 10-30, 21-30, 31-44 and 7-9 of SEQ ID NO:11 or optionally from SEQ ID NO:12, wherein binding of said antagonist to the GIP receptor reduces or inhibits gut glucose uptake after oral glucose administration to a mammal.

56. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising an antibody that binds to GIP receptor with little or no cross reactivity to other gut polypeptide receptors, wherein said antibody is prepared from a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to a contiguous amino acid residue selected from positions 1-30, 16-30, 10-30, 21-30, 31-44 and 7-9 of SEQ ID NO:11 or SEQ ID NO:12, and wherein binding of said antagonist to GIP reduces or inhibits insulin release without significantly affecting serum glucose concentration.

57. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising an antibody that binds to GIP receptor with little or no cross reactivity with other gut insulintropic polypeptides, wherein said antibody is prepared from a polypeptide selected from the group consisting of amino acid sequences having at least 95% identity to a contiguous amino acid residue selected from positions 1-30, 16-30, 10-30, 21-30, 31-44 and 7-9 of SEQ ID NO: 11 to cause little or no insulin release upon administration to a mammal.

58. (new) A glucose-dependent insulintropic polypeptide (GIP) receptor antagonist pharmaceutically acceptable composition comprising an antibody that binds to GIP receptor without cross reactivity to glucagon like peptide-1 (GLP-1) receptor, wherein said antibody is prepared from a polypeptide having at least 95% identity to a contiguous amino acid residue comprising position 7-30 of SEQ ID NO:11 and wherein binding of said antagonist to GIP receptor inhibits insulin release without significantly affecting serum glucose concentration when administered to a mammal.

59. (new) An isolated antibody that binds to glucose-dependent insulintropic polypeptide (GIP) wherein said antibody is prepared from a polypeptide having at least 95% identity to an amino acid residue comprising position 7-30 of SEQ ID NO:11 and wherein said antibody lacks cross reactivity to a glucagon like peptide-1 (GLP-1).

60. (new) A pharmaceutical composition for treating a mammal in need of treatment to improve or normalize glucose tolerance, said pharmaceutical composition comprising:
an effective amount of an antagonist of glucose-dependent insulintropic polypeptide (GIP) for reducing (i) glucose uptake in the gut in the mammal postprandially in the mammal, and (ii) insulin blood levels postprandially in the treated mammal, so that glucose tolerance is improved or normalized in the treated mammal without a need for increased serum insulin, and a pharmaceutically acceptable excipient.

61. (new) An isolated glucose-dependent insulintropic polypeptide (GIP) antagonist that, when administered in an effective amount to a mammal in need of treatment to improve or normalize glucose tolerance, reduces both pancreatic insulin release and circulating insulin blood levels from those levels normally attained in the mammal following a postprandial period without incurring an abnormal elevation in postprandial blood glucose levels and a need for increased serum insulin, so that glucose tolerance is improved or normalized in the mammal.

62. (new) An isolated glucose-dependent insulintropic polypeptide (GIP) receptor antagonist that, when administered in an effective amount to a mammal in need of treatment to improve or normalize glucose tolerance, reduces in the mammal (i) glucose uptake from the

gastrointestinal tract, (ii) pancreatic insulin release and (iii) circulating insulin blood levels, from those levels normally attained following a postprandial period, without incurring an abnormal elevation in postprandial blood glucose levels and a need for increased serum insulin, so that glucose tolerance is improved or normalized in the mammal.

63. (new) An isolated glucose-dependent insulintropic polypeptide (GIP) receptor antagonist that, when administered in an effective amount to a mammal in need of weight loss, reduces in the mammal (i) glucose uptake from the gastrointestinal tract, (ii) pancreatic insulin release and (iii) circulating insulin blood levels, from those glucose and insulin levels normally attained by the mammal following a postprandial period, without incurring in the mammal an abnormal elevation in postprandial blood glucose levels and a need for increased serum insulin, so that the mammal loses weight.

64. (new) An isolated glucose-dependent insulintropic polypeptide (GIP) receptor antagonist that, when administered in an effective amount to a mammal in need of treatment to improve or normalize glucose tolerance for treating non-insulin dependent diabetes mellitus (Type II), reduces in the mammal (i) glucose uptake from the gastrointestinal tract, (ii) pancreatic insulin release and (iii) circulating insulin blood levels from those levels normally attained following a postprandial period, without incurring an abnormal elevation in postprandial blood glucose levels and a need for increased serum insulin, so that glucose tolerance is improved or normalized in the mammal and the mammal is treated for non-insulin dependent diabetes mellitus.

65. (new) An isolated glucose-dependent insulintropic polypeptide (GIP) receptor antagonist that, when administered in an effective amount to a mammal in need of avoiding unacceptable weight gain, reduces in the treated mammal (i) glucose uptake from the gastrointestinal tract, (ii) pancreatic insulin release and (iii) circulating insulin blood levels, from those glucose and insulin levels normally attained by the untreated mammal following a postprandial period, without incurring in the treated mammal an abnormal elevation in postprandial blood glucose levels and a need for increased serum insulin, so that the treated mammal does not incur unacceptable weight gain.

66. (new) An isolated polypeptide comprising an amino acid sequence which specifically interferes with the biological activity of GIP when said polypeptide is administered to an animal in an amount effective to reduce intestinal uptake of glucose and decrease postprandial insulin release, said amino acid sequence comprises amino acids identical to SEQ ID NO:6 and some or all of the amino acids 10-30 from SEQ ID NO:10 .

67. (new) A pharmaceutical composition for treating a mammal in need of treatment to improve or normalize glucose tolerance, said pharmaceutical composition comprising:
a polypeptide comprising an amino acid sequence which specifically interferes with the biological activity of GIP when said polypeptide is administered to a mammal in an amount effective to reduce intestinal uptake of glucose, decrease postprandial insulin release and decrease postprandial glucose levels in the treated mammal, from those insulin levels and glucose levels normally attained in the untreated mammal following a postprandial period, so that glucose tolerance is improved or normalized in the treated mammal, said amino acid sequence comprises amino acids identical to SEQ ID NO:6 and some or all of the amino acids in SEQ ID NO:10, and
a pharmaceutically acceptable excipient.

68. (new) A pharmaceutical composition of claim 67, wherein said postprandial insulin release is decreased in the mammal by up to about 72%.

69. (new) A pharmaceutical composition of claim 67, wherein said postprandial insulin release is decreased in the mammal by at least about 72%.

70. (new) A pharmaceutical composition for treating a mammal in need of treatment to improve or normalize glucose tolerance and reduce weight or avoid unacceptable weight gain, said pharmaceutical composition comprising:

a polypeptide antagonist comprising an amino acid sequence for binding to glucose-dependent insulintropic polypeptide (GIP) receptors in the mammal for antagonizing the biological activity of GIP, said polypeptide antagonist when administered to a mammal in an amount effective (i) reduces intestinal uptake of postprandial glucose, (ii) reduces postprandial

insulin release, (iii) decreases postprandial insulin blood levels and (iv) decreases postprandial glucose blood levels in the treated mammal, from those insulin and glucose blood levels normally attained in the mammal following a postprandial period when the mammal is untreated with said polypeptide antagonist, so that glucose tolerance is improved or normalized and reduced weight is achieved or unacceptable weight gain is avoided in the treated mammal, and
a pharmaceutically acceptable excipient.

71. (new) A pharmaceutical composition of claim 70, wherein said polypeptide antagonist, when administered to the mammal in an amount effective, does not adversely affect the insulintropic effects of a secretagogue in the treated mammal.

72. (new) A pharmaceutical composition of claim 71, wherein said secretagogue is glucagon like peptide-1 (GLP-1).

73. (new) A pharmaceutical composition of claim 71, wherein said secretagogue is arginine.

74. (new) A pharmaceutical composition of claim 71, wherein said secretagogue is glucose.

75. (new) A pharmaceutical composition of claim 70, wherein said amino acid sequence comprises an N-terminal sequence that interferes with functional GIP signaling.

76. (new) A pharmaceutical composition of claim 75, wherein said N-terminal sequence is a hexamer sequence and said hexamer sequence is non-homologous to the N-terminal hexamer sequence of SEQ ID NO:1.

77. (new) A pharmaceutical composition of claim 70, wherein said polypeptide antagonist lacks cross reactivity with glucagon like peptide-1 (GLP-1) receptors.

78. (new) A pharmaceutical composition of claim 70, wherein said polypeptide antagonist does not substantially interfere with the biological activity of glucagon like peptide-1 (GLP-1).

79. (new) An isolated antibody that specifically interferes with the biological activity of glucose-dependent insulintropic polypeptide (GIP), wherein said antibody lacks cross reactivity to a glucagon like peptide-1 (GLP-1).

80. (new) A pharmaceutical composition for treating a mammal in need of treatment to improve or normalize glucose tolerance and reduce weight or avoid unacceptable weight gain, said pharmaceutical composition comprising:

an antagonist for interfering with the biological activity of glucose-dependent insulintropic polypeptide (GIP) in the mammal, said antagonist when administered to a mammal in an amount effective (i) reduces intestinal uptake of postprandial glucose, (ii) reduces postprandial insulin release, (iii) decreases postprandial blood insulin levels and (iv) decreases postprandial blood glucose levels in the treated mammal, from those insulin and glucose blood levels normally attained in the mammal following a postprandial period when the mammal is untreated with said antagonist, so that glucose tolerance is improved or normalized and reduced weight is achieved or unacceptable weight gain is avoided in the treated mammal, and

a pharmaceutically acceptable excipient.

81. (new) A pharmaceutical composition of claim 80, wherein said antagonist lacks cross reactivity with glucagon like peptide-1 (GLP-1) receptors.

82. (new) A pharmaceutical composition of claim 80, wherein said antagonist does not substantially interfere with the biological activity of glucagon like peptide-1 (GLP-1).

83. (new) A pharmaceutical composition of claim 80, wherein the antagonist comprises an antibody that interferes with the biological activity of GIP without interfering with the biological activity of glucagon like peptide-1 (GLP-1).

84. (new) A pharmaceutical composition of claim 80, wherein the antagonist comprises an antibody that binds GIP without interfering with the biological activity of glucagon like peptide-1 (GLP-1).

85. (new) A pharmaceutical composition of claim 80, wherein the antagonist comprises an antibody that binds GIP and an antibody that binds GIP receptor without interfering with the biological activity of glucagon like peptide-1 (GLP-1).